

Alcohol Consumption and Risk of Atrial Fibrillation in Men and Women

The Copenhagen City Heart Study

Kenneth J. Mukamal, MD, MPH, MA; Janne S. Tolstrup, MS; Jens Friberg, MD; Gorm Jensen, MD, DMSc; Morten Grønbaek, MD, PhD, DMSc

Background—The relationship of the full range of alcohol consumption with risk of incident atrial fibrillation has been inconsistent in previous, mainly case-control studies.

Methods and Results—In a prospective cohort study, we studied the association between self-reported alcohol use and incident atrial fibrillation among 16 415 women and men enrolled in the Copenhagen City Heart Study. We ascertained use of beer, wine, and spirits individually at up to 3 study visits with a structured questionnaire. We identified cases of atrial fibrillation by routine study ECGs and a validated nationwide registry of all hospitalizations. A total of 1071 cases occurred during follow-up. Among both women and men, alcohol consumption throughout the moderate range was not associated with risk of atrial fibrillation. However, consumption of 35 or more drinks per week among men was associated with a hazard ratio of 1.45 (95% CI 1.02 to 2.04); few women consumed this amount of alcohol. Approximately 5% of cases of atrial fibrillation among men were attributable to heavy alcohol use. Further adjustment for blood pressure and incident coronary heart disease and congestive heart failure did not attenuate the association (hazard ratio 1.63; 95% CI 1.15 to 2.31).

Conclusions—Heavy alcohol consumption is associated with a higher risk of atrial fibrillation, at least among men. This relationship does not appear to be related to the adverse effects of heavy drinking on coronary heart disease or blood pressure. (*Circulation*. 2005;112:1736-1742.)

Key Words: alcohol ■ fibrillation ■ arrhythmia ■ epidemiology

Substantial evidence indicates that moderate alcohol consumption is associated with a lower risk of cardiovascular disease than abstinence or heavy drinking.^{1,2} Cohort studies also suggest that moderate alcohol use is inversely associated with risk of congestive heart failure.^{3,4} However, although anecdotal evidence implicates episodic heavy drinking as a trigger of atrial fibrillation (AF),⁵ the relationship of the full range of alcohol use with risk of incident AF is less certain.

At least 4 case-control studies have found relatively similar odds of AF among abstainers and moderate drinkers but significantly higher odds of AF among heavier drinkers.^{6–9} A recent cohort study found a higher risk of AF even among men who consumed ≈ 2 drinks per day.¹⁰ However, 2 prospective cohort studies have not confirmed this finding,^{11,12} and Psaty and colleagues¹² found that alcohol use was inversely associated with risk of AF in the Cardiovascular Health Study. Moreover, experimental studies suggest that alcohol administration decreases susceptibility to and duration of AF in canine models.^{13,14} Thus, substantial contro-

versy remains about the relation of alcohol use and risk of AF.

To address the prospective association of alcohol use and risk of AF more fully, we studied more than 16 000 participants of the Copenhagen City Heart Study (CCHS), a population-based cohort study of residents of Copenhagen, Denmark. As part of the study, participants have received routine resting ECGs at 3 examinations, and a national register records diagnoses from all hospitalizations, which provides reliable and valid assessments of incident AF.

Methods

Study Population

The CCHS began in 1976 with an original population sample of 19 698 persons randomly drawn from the Copenhagen Population Register, of whom 14 223 attended an initial examination. After the first examination in 1976 to 1978, this sample (including individuals who did not attend the first examination) was reinvited to participate in 2 more examinations in 1981 to 1983 and in 1991 to 1994. At the second examination in 1981 to 1983, an additional sample of 500

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From the Division of General Medicine and Primary Care (K.J.M.), Beth Israel Deaconess Medical Center, Boston, Mass; Centre for Alcohol Research (J.S.T., M.G.), National Institute of Public Health, Copenhagen, Denmark; The Copenhagen City Heart Study (J.F.), Bispebjerg University Hospital, Copenhagen, Denmark; and the Department of Cardiovascular Medicine (G.J.), Hvidovre University Hospital, Copenhagen, Denmark.

Correspondence to Kenneth J. Mukamal, MD, MPH, MA, Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center, 330 Brookline Ave, RO-114, Boston, MA 02215. E-mail kmukamal@bidmc.harvard.edu

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participants (aged 20 to 24 years) was invited, and at the third examination in 1991 to 1994, a final 3000 subjects (aged 20 to 49 years) were invited. The number of new participants was 14 223 at the first visit, 1563 at the second, and 2360 at the third, for a total of 18 146 individuals. At each of the 3 examinations, participants completed a questionnaire concerning their medical history, socioeconomic status, exercise, smoking, and drinking habits. We excluded participants with prevalent AF on their baseline ECG ($n=118$); those with self-reported coronary heart disease, stroke, use of cardiac medication, or use of antihypertensives at baseline ($n=1431$); and those with missing information on alcohol use ($n=180$), which left us with 16 415 participants eligible for analysis.

The CCHS was approved by the Ethics Committee of Copenhagen and Frederiksberg Municipality, Denmark. New and returning participants gave informed consent verbally at the first 2 examinations (ie, up to 1983) and in writing at each subsequent examination.

Assessment of Alcohol Consumption

Participants reported their alcohol use in standardized interviews. They individually reported their intake of beer (in bottles), wine (in glasses), and spirits (in units), with response categories of "never/hardly ever," "monthly," "weekly," or "daily" and number of drinks per day among daily drinkers. As previously described,^{15,16} less-than-daily intake was estimated from these categories by regression and added to daily intake (of those beverages consumed daily) as needed. In a validation analysis, the age-adjusted correlation coefficients between self-reported alcohol intake and measured levels of HDL cholesterol were 0.20 among men and 0.22 among women ($P<0.001$ for both), similar to findings from other representative cohorts.^{17,18}

We classified participants according to their usual weekly intake of alcohol as in previous studies¹⁹: <1 serving, 1 to 6 servings, 7 to 13 servings, 14 to 20 servings, 21 to 27 servings, 28 to 34 servings, and ≥ 35 servings. Because of the more limited range of intake among women, their highest category of alcohol intake was ≥ 21 servings per week.

Because intake was queried separately for each alcoholic beverage, we could not determine overall drinking frequency in the entire cohort with certainty. Using the response categories noted, we estimated drinking frequency among the subset of participants who predominately consumed a single beverage type ($>90\%$ of their overall alcohol use).

Determination of AF

Participants underwent a resting 12-lead ECG at each study examination. Each ECG was coded according to the Minnesota coding system by 2 independent coders; in cases of dispute, a third coder settled the disagreement. A physician then reviewed and confirmed all ECGs classified as AF. In a randomly chosen sample representing 10% (817/8170) of patients aged ≥ 65 years with ECGs initially coded without AF, only 2 ECGs (0.2%) were recoded as AF on review.²⁰

In addition, the Danish National Hospital Discharge Register records discharge diagnoses from all Danish hospital admissions. We identified first hospitalizations with a diagnosis of AF using International Classification of Diseases, 8th Revision (ICD-8) codes 427.93 and 427.94 through 1993 and International Classification of Diseases, 10th Revision (ICD-10) code I48.9 from 1994 forward.

In a previous validation of this registry, review of a subset of 116 medical records by a cardiologist confirmed the diagnosis in 112 cases.¹⁰ We further assessed the validity of our determinations of AF by review of a random sample of 25 medical records coded with AF and 25 medical records coded with coronary heart disease (but not AF) by a single cardiologist (JF). Three records coded with AF had no evidence of AF during hospitalization (specificity 88%); 3 records coded without AF had ECG evidence of AF (sensitivity 88%).

We also examined the validity of AF diagnoses in 2 additional ways. First, we found an incidence rate of AF after the third examination for adults 65 years and older of 11.6 cases per 1000 person-years; the comparable incidence rate in an older population in the United States during a similar time period was 19.2/1000.¹²

Second, we found that participants with AF diagnosed in this manner had a multivariable-adjusted hazard ratio of stroke (using published criteria²¹) after the diagnosis of AF of 2.62 (95% CI 2.14 to 3.21) among men and 4.85 (95% CI 4.02 to 5.87) among women.

Other Covariates

Arterial blood pressure was measured in the left arm with the patient in the sitting position after 5 minutes' rest. Study staff measured height and weight with subjects dressed in loose-fitting clothing without shoes. We classified participants as having diabetes if they reported a physician-made diagnosis or if they had a nonfasting glucose of 11.1 mmol/L (200 mg/dL) at any examination.

Statistical Analysis

We describe baseline characteristics of CCHS participants with median values for continuous variables and proportions for categorical variables. We tested for homogeneity in baseline characteristics with Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables.

Participants accrued person-time from study entry until their first hospitalization with AF, the first examination at which AF was noted, death, or January 1, 2001. Because we did not have data on hospitalizations before the first study examination (with which to exclude participants in sinus rhythm with a history of AF), we excluded the 2 participants in the original cohort with a diagnosis of AF within 1 year of study entry. In a sensitivity analysis, we set the censoring date for participants with AF diagnosed at each study examination to the median censoring date of participants diagnosed by hospitalization in the preceding time period; this did not change our results.

In initial multivariable Cox proportional hazards regression analyses, we simultaneously adjusted for age, height, body mass index, smoking, physical activity, education, income, family history of cardiovascular disease, cohabitation, FEV₁ (forced expiratory volume in 1 second), and history of diabetes. We assigned indicator variables to participants with missing information on FEV₁ ($n=828$), income ($n=493$), and body mass index ($n=451$); analyses restricted to participants without missing information for covariates yielded very similar results that are not shown here. Age was used as the time axis in Cox models to ensure comparison of individuals at the same age and hence maximize adjustment for age.

To evaluate possible mediators, we performed analyses that additionally adjusted for systolic blood pressure and treated hypertension, incident congestive heart failure, and incident coronary heart disease. Heavy alcohol intake has been identified as a risk factor for each of these variables,²² and all have been associated with risk of AF,¹² which implies that they could explain at least part of an association between alcohol intake and risk of AF. For the latter 2 variables, we used time-varying covariates set to the date of first hospitalization for each diagnosis.

We performed primary analyses using updated measures of alcohol consumption and other covariates, in which we prospectively assessed the risk of AF in between-examination increments, based on determinations of alcohol consumption and other covariates derived from the preceding questionnaire. We assessed the risk associated with individual beverage types in similar fashion. In beverage-specific analyses, we examined the association of individual categories of intake of a given beverage relative to abstinence from that beverage while simultaneously adjusting for the standard covariates that we incorporated into other models and for intake of each of the other 2 beverage types.²³ For tests of linear trend, we treated the median value within categories of alcohol intake as a continuous variable. To explore the dose-response relationship further, we also performed regression analyses using linear splines²⁴ with knots at increments of 3 drinks/wk. We estimated the population-attributable risk related to heavy alcohol intake using standard methods.²⁵

Results

Baseline Characteristics

Table 1 shows the characteristics of participants categorized at baseline according to usual alcohol consumption. Individ-

TABLE 1. Characteristics of 16 415 CCHS Participants Free of Clinical Cardiovascular Disease According to Usual Alcohol Consumption

| | Weekly No. of Drinks | | | | | | | <i>P</i> |
|-------------------------------------|----------------------|-------------|-------------|-------------|-------------------------------|-------------|-------------|----------|
| | <1 | 1 to 6 | 7 to 13 | 14 to 20 | ≥21 (Women) 21 to 27 (Men) | 28 to 34 | ≥35 | |
| Women | n=2631 | n=3969 | n=1461 | n=451 | n=315 | ... | ... | |
| Weekly intake (in drinks) of: | | | | | | | | |
| Beer | 0 | 0.9 | 3.7 | 4.7 | 7.0 | ... | ... | <0.001 |
| Wine | 0 | 1.2 | 4.8 | 5.7 | 14.0 | ... | ... | <0.001 |
| Liquor | 0 | 0 | 1.2 | 1.3 | 4.6 | ... | ... | <0.001 |
| Age, y* | 56 (33, 73) | 50 (25, 68) | 48 (26, 69) | 49 (31, 69) | 50 (33, 68) | ... | ... | <0.001 |
| Education <8 y, % | 61 | 37 | 26 | 30 | 29 | ... | ... | <0.001 |
| Cohabiting, % | 63 | 71 | 70 | 73 | 65 | ... | ... | <0.001 |
| Ever smokers, % | 67 | 72 | 77 | 85 | 85 | ... | ... | <0.001 |
| BMI, kg/m ² | 24.3 | 23.4 | 23.0 | 22.8 | 23.6 | ... | ... | <0.001 |
| Height, cm | 161 | 163 | 164 | 164 | 164 | ... | ... | <0.001 |
| Diabetes, % | 3 | 1 | 1 | 0 | 1 | ... | ... | <0.001 |
| Exercise intensity, % | | | | | | | | |
| None | 26 | 14 | 13 | 20 | 23 | ... | ... | <0.001 |
| Low | 54 | 60 | 57 | 54 | 49 | ... | ... | <0.001 |
| Moderate | 19 | 25 | 28 | 25 | 26 | ... | ... | <0.001 |
| High | 1 | 1 | 2 | 2 | 2 | ... | ... | 0.26 |
| FEV ₁ , mean % predicted | 80.1 | 81.8 | 82.0 | 81.2 | 81.0 | ... | ... | <0.001 |
| Family Hx CVD, % | 33 | 33 | 35 | 41 | 32 | ... | ... | 0.03 |
| Income in lower tertile, % | 44 | 24 | 22 | 22 | 23 | ... | ... | <0.001 |
| Men | n=824 | n=1703 | n=1799 | n=1269 | n=609 | n=435 | n=949 | |
| Weekly intake (in drinks) of: | | | | | | | | |
| Beer | 0.1 | 2.1 | 7.0 | 7.4 | 16 | 28 | 35 | <0.001 |
| Wine | 0 | 1.7 | 1.7 | 3.0 | 2.1 | 1.7 | 1.1 | <0.001 |
| Liquor | 0.1 | 1.0 | 1.7 | 2.0 | 2.0 | 2.0 | 2.0 | <0.001 |
| Age, y* | 54 (31, 75) | 51 (25, 71) | 50 (25, 70) | 50 (26, 70) | 52 (28, 70) | 51 (33, 68) | 50 (33, 68) | <0.001 |
| Education <8 y, % | 54 | 40 | 37 | 36 | 41 | 44 | 50 | <0.001 |
| Cohabiting, % | 71 | 77 | 79 | 77 | 77 | 74 | 68 | <0.001 |
| Ever smokers, % | 83 | 81 | 85 | 89 | 92 | 91 | 93 | <0.001 |
| BMI, kg/m ² | 25.2 | 24.8 | 25.0 | 25.1 | 25.2 | 25.9 | 26.1 | <0.001 |
| Height, cm | 173 | 175 | 175 | 175 | 175 | 174 | 174 | <0.001 |
| Diabetes, % | 5 | 3 | 3 | 3 | 3 | 5 | 4 | 0.08 |
| Exercise intensity, % | | | | | | | | |
| None | 25 | 17 | 15 | 14 | 15 | 22 | 26 | <0.001 |
| Low | 44 | 44 | 48 | 49 | 48 | 45 | 44 | 0.01 |
| Moderate | 28 | 34 | 33 | 32 | 32 | 29 | 26 | <0.001 |
| High | 4 | 5 | 4 | 4 | 4 | 3 | 4 | 0.42 |
| FEV ₁ , mean % predicted | 79.1 | 80.7 | 80.7 | 80.0 | 79.3 | 78.6 | 78.4 | <0.001 |
| Family Hx CVD, % | 30 | 27 | 30 | 28 | 33 | 27 | 30 | 0.09 |
| Income in lower tertile, % | 38 | 25 | 19 | 19 | 17 | 20 | 21 | <0.001 |

BMI indicates body mass index; Family Hx CVD, family history of cardiovascular disease.

Medians and probability values from Kruskal-Wallis tests are shown for continuous variables, and proportions and probability values from χ^2 tests are shown for categorical variables.

*Median (5th percentile, 95th percentile).

uals in the lowest drinking category tended to be older and to have lower income levels, whereas those in the higher drinking categories were more likely to smoke. Women consumed wine in the greatest amount, whereas men chiefly consumed beer.

Average Alcohol Consumption and Risk of AF

We documented 1071 cases of incident AF. Of these 1071, 68 were diagnosed by a study ECG, 891 from hospitalization records, and 112 from both sources. In both age- and multivariable-adjusted analyses, the risk of AF was very

TABLE 2. Hazard Ratios and 95% CIs for Risk of AF According to Usual Alcohol Consumption Among CCHS Participants Free of Cardiovascular Disease

| | Weekly No. of Drinks | | | | | | | <i>P</i> * |
|-------------------------------|----------------------|------------------|------------------|------------------|-------------------------------|------------------|------------------|------------|
| | <1 | 1 to 6 | 7 to 13 | 14 to 20 | ≥21 (Women) 21 to 27 (Men) | 28 to 34 | ≥35 | |
| Women | | | | | | | | |
| Cases | 248 | 148 | 81 | 28 | 18 | ... | ... | |
| Person-years | 59 466 | 63 380 | 27 249 | 9450 | 5970 | ... | ... | |
| Age-adjusted | 1.00 | 0.91 (0.74–1.12) | 1.04 (0.81–1.34) | 1.03 (0.70–1.52) | 1.26 (0.78–2.04) | ... | ... | 0.35 |
| Multivariable model† (95% CI) | 1.00 | 0.89 (0.72–1.09) | 0.99 (0.76–1.28) | 0.96 (0.64–1.43) | 1.04 (0.64–1.70) | ... | ... | 0.87 |
| With mediators‡ | 1.00 | 0.87 (0.70–1.07) | 1.04 (0.80–1.35) | 1.03 (0.69–1.53) | 1.07 (0.65–1.75) | ... | ... | 0.60 |
| Men | | | | | | | | |
| Cases | 81 | 123 | 143 | 75 | 37 | 29 | 60 | |
| Person-years | 15 834 | 29 084 | 30 794 | 19 198 | 9345 | 7049 | 12 688 | |
| Age-adjusted (95% CI) | 1.00 | 0.98 (0.74–1.30) | 1.19 (0.91–1.57) | 1.01 (0.74–1.39) | 1.05 (0.71–1.55) | 1.19 (0.78–1.82) | 1.62 (1.16–2.27) | 0.005 |
| Multivariable model† (95% CI) | 1.00 | 0.96 (0.73–1.28) | 1.16 (0.88–1.53) | 0.95 (0.69–1.31) | 0.98 (0.66–1.45) | 1.06 (0.69–1.64) | 1.45 (1.02–2.04) | 0.05 |
| With mediators‡ (95% CI) | 1.00 | 1.01 (0.76–1.34) | 1.26 (0.95–1.66) | 1.02 (0.74–1.41) | 1.03 (0.69–1.54) | 1.31 (0.85–2.02) | 1.63 (1.15–2.31) | 0.007 |

*Probability values derive from tests of trend.

†The multivariable model adjusted for age, smoking, education, cohabitation, family history of cardiovascular disease, diabetes, income, physical activity, BMI, FEV₁, and height.

‡Mediators included use of blood pressure medication, systolic blood pressure, and incident diagnoses of coronary heart disease and congestive heart failure

similar between abstainers and those who consumed up to 14 drinks per week (Table 2). Among men, we found a higher risk among consumers of 35 or more drinks per week. We did not find a similar risk among women who consumed 21 or more drinks per week, but very few women consumed 28 or more drinks per week (with a total of only 4 cases of AF among such women). Given that 12.5% of men in the CCHS consumed 35 or more drinks per week, we estimate that ≈5% of cases of AF among men were attributable to this level of intake.

In stratified analyses (not shown), we found no evidence of interaction among participants stratified by sex ($P=0.96$), median age (for men, 55.8 years, $P=0.22$; for women, 56.8 years, $P=0.32$), or median body mass index (for men, 25.5 kg/m², $P=0.68$; for women, 24.0 kg/m², $P=0.49$). In all cases, higher risk was generally restricted to men who drank heavily. In exploratory analyses, using linear splines, of the dose-response relationship among men, there appeared to a threshold relationship similar to that suggested by analyses of alcohol intake in categories. The risk of AF increased notably at a threshold of ≈35 drinks per week, with a relatively flat relationship at lower levels of intake.

Potential Mediators of the Alcohol-AF Relation

We assessed a series of potential mediators of the association of heavy alcohol intake with risk of AF, including blood pressure, incident coronary heart disease during follow-up, incident congestive heart failure during follow-up, and all 3. As expected, all 3 were strongly and independently associated with risk of AF. However, adjustment for these factors individually or together had relatively little effect on our results, consistent with the hypothesis that these factors do not mediate the relation of alcohol use and AF. For example, the relative risk of AF among men who consumed 35 or more drinks per week was 1.45 in the basic model (as noted above)

and 1.63 (95% CI 1.15 to 2.31) with further adjustment for all 3 factors (Table 2).

Because the association of intake of 28 to 34 drinks per week with risk of AF was stronger after adjustment for mediators, we conducted a post hoc analysis that grouped all men who consumed 28 or more drinks per week. In this analysis, the hazard ratio for drinking 28 or more drinks per week was 1.29 (95% CI 0.95 to 1.77) with multivariable adjustment and 1.50 (95% CI 1.10 to 2.06) after the inclusion of potential mediators. Given the latter hazard ratio, ≈8% of cases of AF among men were attributable to intake of 28 or more drinks per week after adjustment for mediators.

Exploratory Analyses of Beverage Type and Drinking Frequency

Table 3 shows results from exploratory beverage type analyses. There were no statistically significant associations identified. It appeared that consumption of 21 or more drinks per week of both beer and spirits tended to be related to higher risk of AF than found with abstention from these beverages among men.

We found no clear evidence that drinking frequency was related to risk of AF in either women or men (data not shown). This finding was consistent in analyses adjusted for age, for all covariates, and for all covariates with additional adjustment for overall quantity of alcohol use.

Discussion

In this prospective cohort study, alcohol intake of 35 or more drinks per week was associated with a higher risk of AF, at least among men. Previous studies of the relation of alcohol use and risk of AF have not yielded consistent results. In a case-control study from the UK General Practice Research Database, Ruigomez and colleagues⁹ found that physician-reported alcohol use above 42 U per week was associated

TABLE 3. Adjusted Hazard Ratios for Risk of AF According to Updated Consumption of Individual Alcoholic Beverages

| | Weekly No. of Drinks | | | | | |
|-----------------------|----------------------|------------------|------------------|-------------------------------|------------------|----------|
| | <1 | 1 to 6 | 7 to 13 | ≥14 (Women) 14 to 20 (Men) | ≥21 | <i>P</i> |
| Women | | | | | | |
| Beer | | | | | | |
| Cases | 272 | 129 | 14 | 8 | ... | |
| Person-years | 104 854 | 50 484 | 7067 | 3110 | ... | |
| Hazard ratio (95% CI) | 1.00 | 1.04 (0.83–1.30) | 0.65 (0.38–1.12) | 1.04 (0.51–2.13) | ... | 0.36 |
| Wine | | | | | | |
| Cases | 316 | 160 | 30 | 17 | ... | |
| Person-years | 78 983 | 71 646 | 9275 | 5612 | ... | |
| Hazard ratio (95% CI) | 1.00 | 0.95 (0.76–1.19) | 1.09 (0.73–1.62) | 1.13 (0.68–1.88) | ... | 0.70 |
| Spirits | | | | | | |
| Cases | 395 | 92 | 29 | 7 | ... | |
| Person-years | 116 140 | 42 229 | 5454 | 1692 | ... | |
| Hazard ratio (95% CI) | 1.00 | 0.85 (0.65–1.09) | 1.11 (0.75–1.65) | 1.19 (0.55–2.57) | ... | 0.58 |
| Men | | | | | | |
| Beer | | | | | | |
| Cases | 123 | 212 | 92 | 52 | 69 | |
| Person-years | 24 274 | 45 758 | 24 182 | 12 454 | 17 323 | |
| Hazard ratio (95% CI) | 1.00 | 1.12 (0.88–1.42) | 1.01 (0.76–1.34) | 1.06 (0.75–1.48) | 1.27 (0.92–1.74) | 0.26 |
| Wine | | | | | | |
| Cases | 288 | 203 | 37 | 13 | 7 | |
| Person-years | 53 260 | 58 105 | 7862 | 3190 | 1575 | |
| Hazard ratio (95% CI) | 1.00 | 0.85 (0.69–1.05) | 0.97 (0.67–1.39) | 0.81 (0.45–1.43) | 0.99 (0.46–2.13) | 0.65 |
| Spirits | | | | | | |
| Cases | 269 | 220 | 49 | 25 | 14 | |
| Person-years | 58 027 | 53 766 | 7592 | 2766 | 1842 | |
| Hazard ratio (95% CI) | 1.00 | 1.06 (0.86–1.31) | 0.92 (0.67–1.28) | 1.19 (0.76–1.87) | 1.47 (0.85–2.56) | 0.26 |

Probability values derive from tests of trend. Hazard ratios were adjusted for age, smoking, education, cohabitation, family history of cardiovascular disease, diabetes, income, physical activity, body mass index, FEV₁, height, and intake of the other 2 beverages.

with an OR of 2.4, with no evidence for an inverse association at lower levels of consumption. An innovative case-control analysis of the Framingham Study that incorporated person-time contributed to the study found an OR of 1.34 (95% CI 1.01 to 1.78) among consumers of more than 36 g (\approx 3 drinks) of alcohol daily but not at lower levels of intake.⁶ In a case-control study from Helsinki, consumption of more than 30 g/d was acutely associated with onset of AF, whereas lighter consumption was not associated with risk.⁸ An analysis of the Diet, Cancer, and Health cohort found 25% to 46% higher risks of AF associated with average intake of \approx 20 g/d or more among men but not among women.¹⁰ In sharp contrast to these studies, Psaty and colleagues¹² found alcohol use to be inversely associated with risk of AF in a 3-year follow-up study of the original Cardiovascular Health Study cohort. To the best of our knowledge, ours is the first prospective cohort study to support the findings of earlier case-control studies that suggested a higher risk restricted to heavy drinking.

The one previous study that assessed beverage type found no differences in risk,¹⁰ despite some evidence that antioxi-

dants can modify AF risk. Mihm and colleagues²⁶ found that patients with AF have higher levels of 2 markers of oxidative stress in right atrial myofibrillar isolates than do patients without AF undergoing cardiac surgery. The same group subsequently found that ascorbate, an antioxidant, alleviated the pacing-induced shortening of the atrial effective refractory period in dogs and that supplemental ascorbate was associated with an adjusted OR of 0.34 (95% CI 0.10 to 1.19) for postoperative AF among patients undergoing CABG surgery.²⁷ In the present study, only the heaviest level of overall alcohol intake was associated with higher risk, and no single beverage was consumed in sufficient amounts to compare their respective effects at that level of consumption with confidence. Further studies, and perhaps meta-analyses of existing studies, are needed to clarify this issue.

Heavier drinkers could sustain a higher risk of AF in a few related ways. First, chronic heavy alcohol use itself could affect atrial structure and size as a direct cardiotoxin, an effect suggested in rat models.²⁸ Second, chronic heavy drinking could have direct proarrhythmic effects. Third, heavier drinkers are likely to have repeated exposure to episodic heavy

drinking (ie, binge drinking), which could increase the risk of triggering a single episode of AF. To support this, porcine models show that acute alcohol administration increases the inducibility of AF, but mainly at very high blood alcohol concentrations.²⁹ Fourth, alcohol consumption could cause brief and otherwise asymptomatic episodes of AF to become persistent. A case-crossover study of patients with acute AF could best assess this distinction³⁰ but would not change the importance of avoiding heavier drinking.

Specific limitations of the present study warrant discussion. As in any observational study, our results could be influenced by differences between participants in factors other than alcohol consumption for which we did not control. For example, we did not have data on dietary factors other than ethanol, although little is known about how such factors affect risk of AF; this limitation may particularly affect beverage type analyses.³¹ To have influenced our primary results, any uncontrolled confounder would need to be associated with both alcohol consumption and risk of AF and generally be unrelated to the other covariates in our multivariable models.

Although we relied on self-reported alcohol consumption in this study, the measures used to estimate alcohol consumption have been found to be valid when compared with a formal dietary interview in Danish populations.³² Furthermore, we found a correlation of alcohol use and HDL cholesterol of the expected magnitude.³³

We relied on a hospital registry and periodic study-related ECGs to document cases of AF. Because study examinations occurred every 5 to 10 years, it is likely that we missed some cases of AF among participants who were not hospitalized during the follow-up period.

Although the CCHS is a population-based cohort study with a high participation rate, participants are nearly all white, native-born Danish adults. As a result, our results must be generalized to other populations with an appropriate degree of caution.

Although we found that risk of AF appeared to be higher only among consumers of 35 drinks per week, it is difficult to determine the exact nature of the dose-response relationship, especially at high levels of intake that were relatively uncommon, although we explored this with spline analyses that provided similar findings. This was especially true for analyses of individual beverage types, because consumption of any individual beverage was limited in many cases. We also lack power to exclude a modest increase in risk associated with moderate drinking, although our data suggest that there is not a substantially increased risk associated with moderate intake.

In summary, alcohol consumption of 35 or more drinks per week was associated with an increased risk of AF among men in a population-based cohort of more than 16 000 adults. This finding supports the widely held, but rarely examined, clinical observation that heavy alcohol use can lead to AF and confirms the cardiotoxic effects of heavy drinking. Studies on the effects of alcohol use on patients with established AF are still needed.

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Kenneth J. Mukamal, Janne S. Tolstrup, Jens Friberg, Gorm Jensen and Morten Grønbaek

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